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# NDA: 21-153

# Clinical Pharmacology with Biopharmaceuticals Review

# September 18, 2000

# Clinical Pharmacology and Biopharmaceutics Review

**NDA: 21-153** **Code: 2S**

**Trade Name**: Nexium™ Delayed-Release Capsules **Stamp Date**: 12/3/1999

**Active Ingredient**: Esomeprazole Sodium **Related INDs**: ——

**Sponsor**: AstraZeneca Pharmaceuticals

**Statistics Consultant**: Donald J. Schuirmann

**Reviewer**: Suliman I. Al-Fayoumi, Ph.D.

**Type of Submission**: Original NDA (NME)

## Synopsis

Esomeprazole (H 199/18), the S-enantiomer of omeprazole, is a potent inhibitor of gastric Acid secretion. It has been proposed for the treatment of a variety of acid-related diseases such as gastroesophageal reflux disease (GERD) and erosive esophagitis (EE).

The sponsor has adequately characterized the clinical pharmacology and biopharmaceutics-related aspects of the drug. H 199/18 is well absorbed with an absolute bioavailability of 90% after repeated-dose administration. The extent of exposure (AUC) for H 199/18 correlates well with inhibition of gastric acid secretion, indicating that response is dose-related.

H 199/18 is highly bound to plasma proteins (97%). It is extensively metabolized by hepatic CYP-450 isozymes, primarily CYP 2C19 and CYP 3A4, to hydroxy and sulphone metabolites. Up to 80% of the oral dose is excreted as inactive metabolites in the urine. Additionally, less than 1% of the oral dose is excreted in urine as unchanged drug. Dosage adjustment is warranted for H 199/18 in moderate and severe hepatic dysfunction, but not in renal failure. Total clearance of H 199/18 is reduced from 17 L/hr after a single dose to 9 L/hr after repeated-dose administration indicating that H 199/18 exhibits time-dependent pharmacokinetics. The AUC for H 199/18 is reduced by 44% after food intake indicating a significant food effect.

$C_{max}$ and AUC of H 199/18 were elevated in elderly and female subjects relative to young male subjects. The clinical trial- and to-be-marketed formulations were shown to be bioequivalent.

Significant metabolic drug-drug interactions were shown for H 199/18 with diazepam and clarithromycin.

**Recommendations:**

The Human Pharmacokinetics and Bioavailability section of NDA 21-153 submitted on 12/6/1999 is acceptable from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics. Clinical Pharmacology and Biopharmaceutics-related changes to the sponsor's proposed labeling needs to be conveyed to the sponsor as deemed appropriate.

/S/ 9/18/00

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Suresh Doddapaneni, Ph.D., Team leader /S/ 9/18/00

cc: HFD-180: NDA 21-153 (1x); DIV FILE (1x); MWALSH (1x); SDODDAPANENI (1x); SALFAYOUMI (1x); HFD-870 SHUANG (1x); CDR: ATTN Zom Zadeng

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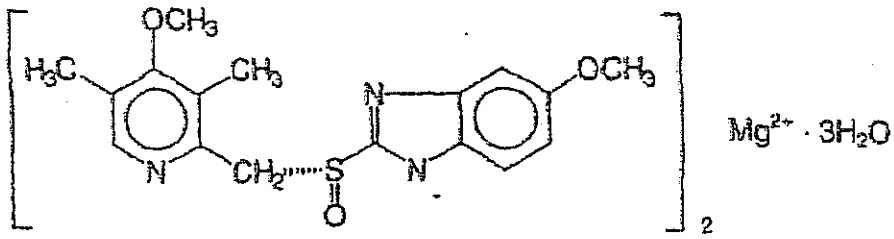
# TABLE OF CONTENTS

# SUMMARY

## 1. What is the pharmacological class, scientific rationale and intended use of H 199/18 (esomeprazole)?




H 199/18 is the S-enantiomer of omeprazole, a potent inhibitor of gastric acid secretion and the first proton pump inhibitor approved in the US in 1989. *In vitro* studies as well as animal studies have demonstrated equipotent activity of omeprazole and its two enantiomers on gastric acid secretion. As omeprazole treatment has not been successful in all patients with acid-related diseases, H 199/18 was developed by AstraZeneca Pharmaceutical Company with the intention of further optimizing the treatment of acid-related diseases. At present, H 199/18 is not approved in any country, [redacted]

The sponsor's proposed indications include; healing and maintenance of Erosive Esophagitis, treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD) [redacted] The proposed dosage is either 20 or 40 mg once daily for 4-8 weeks.

## 2. What are the physicochemical properties of H 199/18 and the composition of the to-be-marketed (TBM) capsule formulation?

*Esomeprazole is highly unstable in acidic media, therefore it has been formulated as enteric-coated pellets.*

The partition coefficient for H 199/18 between n-octanol and water was determined as log $K_D$ = 2.24. The stable form in water for H 199/18 megnesium is a trihydrate. The solubility of H 199/18 magnseium trihydrate in water is 1.5 mg/ml with a corresponding pH of 10.0.

Esomeprazole magnesium has been formulated as delayed-release capsules for oral administration. Each capsule contains 20 mg or 40 mg esomeprazole formulated in enteric-coated pellets. The two strengths are compositionally proportional. The composition of the formulation for each strength is shown in table 1.

Table 1. Composition of the TBM Nexium capsule

| Ingredients | 20 mg Capsule (mg) | 40 mg Capsule (mg) | Function |
|---|---|---|---|
| H 199/18 (as H 199/18 magnesium trihydrate) | 20 (22.3) | 40 (44.5) | *Active ingredient* |
| Glyceryl monostearate 40-50 | | | |
| Hydroxypropyl Cellulose | | | |
| Hydroxypropyl Methylcellulose | | | |
| Magnesium Stearate | | | |
| Methacrylic Acid Copolymer Type C | | | |
| Polysorbate 80 | | | |
| Sugar spheres | | | |
| Talc | | | |
| Triethyl Citrate | | | |
| Hard gelatin capsules | | | |

3. **Is there a pharmacokinetic/pharmacodynamic relationship for H 199/18?**

*The % inhibition of pentagastrin-stimulated acid secretion showed good correlation with AUC (exposure) of H 199/18, with a lower AUC needed for maximal inhibition of acid secretion on day 5 relative to day 1.*

A dose-response study of H 199/18 sodium on pentagastrin-stimulated gastric acid secretion in healthy subjects at doses of 5, 10 and 20 mg showed that the antisecretory effect of H 199/18 is dose dependent, with an increased effect upon repeated daily dosing which is likely related to the cumulative effect of H 199/18 on the inhibition of gastric acid secretion (Study QBE-0002).

A second study compared 20 mg omeprazole to 20 and 40 mg H 199/18 on the effect on 24-hour intragastric pH and %time with pH > 4. The study failed to demonstrate a clear advantage of H 199/18 over omeprazole at a dose of 20 mg. In addition, the 40 mg dose of H 199/18 proved to be more effective than the 20 mg dose in elevating 24-hour intragastric pH as well as increasing %time with pH > 4 (Study QBE-0008). It is unclear, however, whether the observed differences in the pharmacodynamic markers would translate into clinically relevant differences in patients.

4. **Were there any dose-related adverse events?**

*No dose-related serious adverse events were observed during the course of the clinical studies.*

## Study SH-QBE-0008

### Objectives

- To compare H 199/18 20 mg with omeprazole 20 mg with respect to their effects on intragastric pH in patients referred for investigation of or with established GERD.
- To compare H 199/18 40 mg with H 199/18 20 mg and with omeprazole 20 mg with respect to their effects on intragastric pH, and to study the PK of H 199/18 and omeprazole. In addition, the bioavailability of the 20 mg dosage forms of H 199/18 and omeprazole will be compared.

### Study Design

Double-blind, randomized, three-way cross-over study in patients.

| | |
|---|---|
| **Subjects** | 36 subjects (15 males and 21 females, age 45.2 yrs) |
| **Treatments** | Subjects were randomized to receive each of the following 3 treatment groups once daily over a 5-day period: 20 and 40 mg H 199/18 capsules and 20 mg omeprazole enteric-coated capsule formulation. |
| **Washout Period** | at least 2 weeks |
| **PK Sampling** | Samples were collected for determination of H 199/18 in plasma before and at the following time points postdose: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hrs |
| **Intragastric pH Test** | After two 15-min collections of basal secretion, pentagastrin (90 µg/hr) was administered IV and stimulated gastric acid secretion was collected for another four 15-min periods. |
| **Analytical Assay** | The assay consisted of [redacted]<br>Plasma samples were analyzed according to methods [redacted]<br>determination of H 199/18 and omeprazole (LOQ = [redacted] |

### Pharmacokinetics/Pharmacodynamics

The following pharmacokinetic parameters were estimated using non-compartmental analysis: $t_{max}$, $C_{max}$, $K_e$, $AUC_{0-t}$, $AUC_{0-\infty}$, and $t_{1/2}$.

The maximum acid response to pentagastrin simulation was measured as peak acid output (PAO), calculated as the sum of the two highest consecutive 15-min samples multiplied by two and expressed as mmol/L.

The % Change in PAO after drug intake was calculated relative to the control acid secretion test before drug intake.

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## Results

Table 2. Summary of the mean primary PK and PD parameters for each treatment

| PK/PD Parameter | Omeprazole 20 mg | H 199/18 20 mg | H 199/18 40 mg |
|---|---|---|---|
| **PK** | | | |
| Cmax (µmol/L) | 1.41 | 2.42 | 5.13 |
| $t_{max}$ (hr) | 1.0 | 1.0 | 1.2 |
| $t_{1/2}$ (hr) | 1.0 | 1.3 | 1.6 |
| $AUC_{0-\infty}$ (µmol·h/L) | 2.34 | 4.18 | 12.64 |
| **PD** | | | |
| % time at pH>4 | 43.72 (36.74-50.71)† | 53.01 (46.03-59.99)† | 69.83 (62.85-76.81)† |
| Median 24-hr pH | 3.58 (3.22-3.94)† | 4.14 (3.78-4.50)† | 4.88 (4.52-5.24)† |

† 95% Confidence interval.

## Reviewer's Comments

- *Based on the PD markers utilized as measures of the effectiveness of each of the treatments in reducing intragastric acidity, there seems to be a relationship between exposure (AUC) of H 199/18 and effect (reduction in intragastric acidity). H 199/18 40 mg, as might be expected, is superior to the 20 mg dose of both H 199/18 and omeprazole. Despite a trend for an enhanced effectiveness by H 199/18 20 mg compared to omeprazole 20 mg, the confidence intervals of both treatments significantly overlap, thus obscuring interpretation of the inter-treatment differences. Therefore, it may not be concluded based on the results of the current study that H 199/18 is more effective than omeprazole at a dose of 20 mg.*

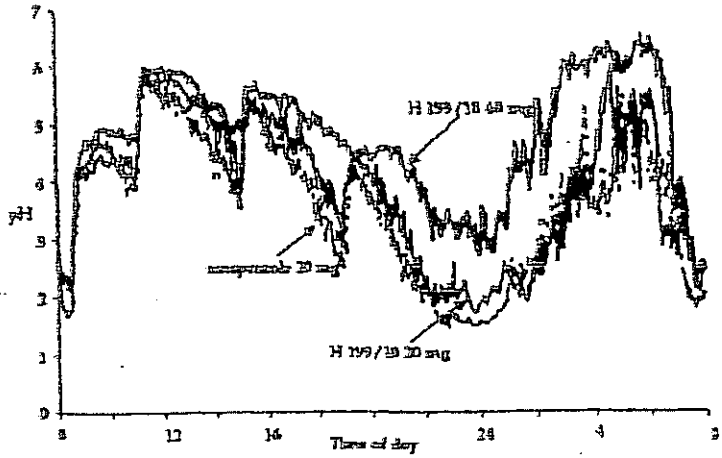


Figure 2. Median 24-hour pH-profiles in patients with symptomatic GORD, n=36.